UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 627. Pynamin Forte. Review of Rabbit Developmental Toxicity Tests: Range-Finding and Main Studies.

Tox. Chem. No. 025B
Project Nos. 1-2060 and 1-2062

TO: Richard King, PM Team # 72
Special Review and
Reregistration Division (H7508W)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 11/26/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head Roger L. Gardner
Section I, Toxicology Branch I
Health Effects Division (H7509C) 12-3-91 KB 12/11/91

Record No(s). S397619 and S397623

Background and Request:

In response to the Registration Standard on Allethrins, Sumitomo Chemical Company has submitted a developmental toxicity range-finding study and a full developmental toxicity study on rabbits with Pynamin Forte. The Toxicology Branch (TB-I) has been asked to review the submitted studies.

Toxicology Branch Response:

TB-I has reviewed the range-finding study and the full developmental toxicity study in rabbits on Pynamin Forte. The range-finding study is classified as Core Supplementary and the full study is classified as Core Guideline. The full study satisfies the regulatory requirement for a developmental toxicity study in rabbits on Technical Pynamin Forte. The following paragraphs are short summaries of the results of the studies.

Pynamin Forte was tested in a range-finding developmental toxicity study in rabbits at the following dose levels: 0, 50, 100, 200 and 300 mg/kg/day. The NOEL for maternal toxicity was close to 300 mg/kg/day. The only effects observed at that dose level were a non-significant decrease in body weight gain during gestation and a significant decrease in food consumption on days

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7-20 of gestation. Therefore, the NOEL is 200 mg/kg/day and the LEL is 300 mg/kg/day. There were no observed developmental effects with this chemical at the dose levels tested; however, it is noted that only external examinations were conducted on the fetuses. The NOEL for developmental toxicity is 300 mg/kg/day (HDT).

Pynamin Forte was tested in a developmental toxicity study in rabbits. The following dose levels were used: 0, 30, 100 and 350 mg/kg/day. The NOEL for maternal toxicity is 100 mg/kg/day and the LEL is 350 mg/kg/day (death, clinical signs, decrease in body weight gain and food consumption during dosing period and gastric lesions). The NOEL for developmental toxicity is 100 mg/kg/day and the LEL is 350 mg/kg/day (increased incidences of rib/rib-vertebral malformations).

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DATA EVALUATION REPORT

STUDY TYPE: Teratology - Developmental Toxicity Range-Finding

SPECIES: Rabbits

TOX. CHEM. NO./CASWELL NO.: 025B

ACCESSION NUMBER/MRID NO.: 412258-05

TEST MATERIAL: Pynamin Forte

SYNONYMS: D-cis/trans allethrin

STUDY NUMBER(S): KT-91-0096

REPORT NUMBER: Argus Protocol 119-006P

SPONSOR: Sumitomc Chemical Company, Ltd., Osaka, Japan

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, PA

TITLE OF REPORT: Range-Finding Teratology Study in Rabbits

AUTHOR(S): A.M. Hoberman

REPORT ISSUED: 7/17/89

CONCLUSION: Pynamin Forte was tested in a range-finding developmental toxicity study in rabbits at the following dose levels: 0, 50, 100, 200 and 300 mg/kg/day. The NOEL for maternal toxicity was close to 300 mg/kg/day. The only effects observed at that dose level were a non-significant decrease in body weight gain during gestation and a significant decrease in food consumption on days 7-20 of gestation. Therefore, the NOEL is 200 mg/kg/day and the LEL is 300 mg/kg/day. There were no observed developmental effects with this chemical at the dose levels tested. The NOEL for developmental toxicity is 300 mg/kg/day (HDT).

Classification: Supplementary

Testing Guideline Satisfied: None

A. MATERIALS AND METHODS:

1. Test Compound(s)

Chemical Name: 36.5% allyl homolog of cinerin I and 55.5% other allethrin stereoisomers

Description: Amber colored liquid
Batch #(s), Other #(s): Lot 50310
Purity: 93.4%
Source: Sumitomo Chemical Company, Ltd.
Vehicle (if applicable): aqueous 0.5% (w/w) methylcellulose

2. Test Animals

Species and Strain (sexes): Male and female New Zealand White [Hra:(NZW)SPF] rabbits
Age: 5 months and 3 weeks at start of study.
Weight(s): 3.1 - 3.56 kg (females)
Source(s): Hazleton Research Animals, Denver, PA

3. Study Design:

This study was a range-finding study designed to determine the maternal and/or developmental toxicity potential of pynamin forte when administered by stomach tube to rabbits on gestation days 7 through 19, inclusive, in order to identify dosage levels to be used in an expanded developmental toxicity study.

a. Mating:

Natural or artificial insemination? artificial. Describe technique used: Each rabbit was injected with 20 USP Units/kg of Human Chorionic Gonadotropin (HCG) i.v. approximately 3 hours prior to insemination. Each rabbit was inseminated with an estimated 6.0×10^6 spermatozoa. The day artificial insemination was performed was designated as day 0 of presumed gestation.

b. Group Arrangement:

Test Group	Dosage (mg/kg/day)	Pynamin Forte Concentration (mg/ml)	Dosage Volume (ml/kg)	No. Assigned
I	0	0	10	7
II	50	5	10	7
III	100	10	10	7
IV	200	20	10	7
V	300	30	10	7

c. Dosing:

All doses were in a volume of 10 ml/kg of body weight/day. Dosing was based on the 7th gestation day body weight.

1) Basis For Selection of Dose Levels: Not stated, but this is a range-finding study being conducted in order to select dose levels for the main study.

2) Preparation: The appropriate amount of the test chemical was weighed out and a sufficient amount of vehicle was added to achieve a total weight of 500 grams. The container was capped, shaken and blended, allowed to stand to allow air bubbles to dissipate and stirred prior to dosing.

3) Frequency of Preparation: Daily

4) Storage Conditions: The test substance was kept in a cool, dry, well ventilated area and protected from heat.

5) Stability Analyses: Stability of the test substance was on file with the sponsor and was not provided in the report.

6) Homogeneity Analyses: Conducted on the lowest and highest concentrations used in the study. Samples were taken from the top, middle and bottom of the sample mixture.

7) Concentration Analyses: Duplicate 10 ml samples of each prepared batch were frozen immediately after each daily preparation. One of the 2 samples taken from each concentration prepared on the first day and the last day of dosage was sent frozen to Lancaster Laboratories, Lancaster, PA.

d. Maternal Examinations:

1) Clinical Observations and Mortality: All female rabbits were observed for appearance and general behavior daily during the prestudy period. The does were observed twice daily for viability during the acclimation, dosing and postdosing periods. Observations for clinical signs of toxicity, abortion or death were made several times each day of dosing (approximately 0.25, 0.5, 1, 2, 3 and 4 hours postdosage during the first 6 days of administration; approximately 0.25, 0.5 and 1 hour postdosage for the remaining days of administration) and then once daily each day of the postdosage period.

2) Body Weight Determinations: Body weights were measured weekly during acclimation, on day 0 and then daily during the dosage and postdosage periods.

3) Food Consumption: Food consumption was measured daily during throughout the study.

4) Gross Necropsy:

Animals which died or were sacrificed in moribund condition prior to end of exposure period and were subjected to complete gross pathological examinations: All does. The cause of death was recorded when possible. The ovaries and uterine contents were examined to the extent possible. All gross lesions were preserved in formalin for possible future evaluation.

Animals sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All does. All gross lesions were preserved in formalin for possible future evaluation.

5) Uterine Examinations: The following observations were recorded:

Number of corpora lutea
Number of live fetuses
Number of dead fetuses
Early and late resorptions
Total implantations
Individual fetal weights
Litter size

e. Fetal Examinations:

The fetuses were examined in the following manner: The fetuses were removed from the uterus, weighed, individually identified by litter and uterine placement and examined for gross external alterations. Live fetuses were sacrificed and sexed. Abnormal fetuses were preserved in isopropyl alcohol and normal fetuses were discarded.

f. Historical Control Data:

Historical control data were not provided to allow comparison with concurrent controls.

g. Statistical analysis:

The following statistical analysis methods were employed: parametric and nonparametric tests. These include Bartlett's (test for homogeneity of variance), analysis of variance (ANOVA - for homogeneous data), Dunnett's (if ANOVA significant), Kruskal-Wallis (nonparametric, not including proportion data, <= 75% ties), Dunn's test (if Kruskal-Wallis test is significant), Fisher's exact test for > 75% ties, variance test for homogeneity of the bionomial distribution (proportion data) and the Terpstra-Jonckeere test for trend. Data obtained from nonpregnant and found dead does were excluded from statistical analyses. The litter was used as the experimental unit.

h. Compliance:

A signed Statement of Confidentiality Claim was provided (only on the basis of its falling within the scope of FIFRA. The document is considered to be confidential and trade secret information in all other countries and for all purposes other than those enunciated in FIFRA.

A signed Statement of compliance with EPA GLP's was provided.

B. RESULTS:

1. Dosage Preparation: For the 30 mg/ml level, the 2 samples were both 4.0% above the target concentration; for the 20 mg/ml level, one sample was 0.5% and the other sample was 4.0% above the target concentration; for the 10 mg/ml level, the samples were 1.5% and 5.2% below the target concentration and for the 5.0 mg/ml level, both samples were 5.6% below the target concentration. The actual concentrations were acceptably close to the target concentrations.

Testing of the homogeneity samples resulted in an average relative standard deviation of 2.38% for the 2.0 mg/ml level, 5.5% for 3.0 mg/ml, 1.1% for 5.0 mg/ml, 8.56% for 60.0 mg/ml, 2.02% for 80.0 mg/ml and 1.03% for the 100 mg/ml level. The samples were acceptably homogeneous.

2. Maternal Toxicity:

a. Clinical Observations and Mortality: There were no treatment-related mortalities. Two does died due to intubation errors: 1 in the 100 mg/kg/day group and 1 in the 200 mg/kg/day group. The right diaphragmatic lobe in the lungs was perforated in each doe. There were no treatment-related clinical signs of toxicity. None of the signs observed were dose-related. Occasionally observed clinical signs included red substance present in the cage pan (impending delivery - 50 mg/kg/day), dyspnea (50 and 300 mg/kg/day) and alopecia (control 100 - 300 mg/kg/day).

b. Body Weight Determinations: Mean body weight gain was inhibited in the 300 mg/kg/day group during days 7 - 10 of gestation when compared to control values. The effect was not statistically significant; however, the authors stated that it

was sufficiently severe to result in a small inhibitory effect on average maternal body weight for days 7 - 17 of gestation when compared to controls. Mean maternal body weights did not differ significantly at any time during the study. The investigators supplied the following data:

Table I: Mean Body Weight Gains (Kg)[a]

Group:	Days 0 - 7	Days 7 - 18	Days 20 - 29	Days 7 - 29
Control	0.21	0.04	0.18	0.39
50	0.33	0.05	0.10	0.31
100	0.30	0.03	0.14	0.34
200	0.31	0.07	0.22	0.45
300	0.26	0.00	0.24	0.44

a = Data extracted from (study or report number Argus 1119-006P and table 4)

c. Food Consumption: During the dosing period, a statistically significant decrease in mean food consumption relative to body weight values (g/kg/day) was observed at the highest dose level (days 7-14, 7-17, 7-20 and 10-14). When calculated as grams of feed consumed/day, the values were lowered but were not statistically significant (days 7-20).

d. Gross Pathology: No treatment-related gross lesions were observed. Occasional observations included hemorrhagic areas in the lungs (1 - 50 mg/kg/day), agenesis of the intermediate lobe in the lungs (1 each - 100 & 200 mg/kg/day), accessory splenic tissue (1 each - 50, 200, 300 mg/kg/day), swollen vulva (1 - 300 mg/kg/day) and parovarian cysts (all groups, 2, 4, 6, 2 and 3 in control, 50, 100, 200 and 300 mg/kg/day, respectively).

e. Cesarean section Observations: There were no treatment-related differences between the control and treated groups in the number of corpora lutea, implantations, litter sizes or resorptions, in the percentages of live male fetuses/litter and in fetal body weights/litter. In addition, the incidences of does with resorptions and of does with litters including live fetuses were unaffected by administration of the test substance. The following table summarizes the findings.

Table III: Cesarean Section observations[a]

Dose: mg/kg/day	0	50	100	200	300
#Animals Assigned	7	7	7	7	7
#Animals Mated/Inseminated	7	7	7	7	7
Pregnancy Rate (%)	6 (85.7)	7 (100)	6 (85.7)	6 (85.7)	7 (100)
Maternal Wastage					
#Died	0	0	1	1	0
#Died/pregnant	0	0	1	1	0
#Non pregnant	1	0	1	1	0
#Aborted	0	0	0	0	0
#Premature Delivery	0	0	0	0	0
Corpora Lutea/Doe	9.3	9.3	9.4	10.2	12.1
Implantations/Doe	6.7	6.7	4.2	6.2	8.0
Implantation Efficiency (%)[b]	70.3	75.8	45.0	61.2	68.4
Litter Size/Doe	6.2	6.3	4.2	6.0	8.0
Live Fetuses/Doe	6.2	6.3	4.2	6.0	8.0
Dead Fetuses/Doe	0.0	0.0	0.0	0.0	0.0
Resorptions/Doe					
Early	0.5	0.3	0.0	0.2	0.0
Late	0.0	0.1	0.0	0.0	0.0
Does With Any Resorptions (%)	3 (50)	3 (42.8)	0 (0)	1 (20)	0 (0)
Does With All Conceptuses Resorbing (%)	1[c] (16.7)	0 (0)	0 (0)	0 (0)	0 (0)
Does With Viable Fetuses (%)	5 (83.3)	7 (100)	5 (100)	5 (100)	7 (100)
Mean Fetal Weight (grams/litter)	44.73	44.63	52.13[d]	48.92	47.65
Sex Ratio (% Live Male) per Litter	57.7	51.0	37.7	44.2	44.5

[a] = Data extracted from (study or report number Argus 1119-006P and table 8)

[b] = Implantation Efficiency is the number of implantation sites divided by the number of corpora lutea multiplied by 100.

[c] = One control doe had a litter which consisted of one early resorption.

[d] = A statistically significant increase (P<=0.01) in average fetal body weight in female fetuses observed. Attributed to the relatively smaller live litter size in this dose group.

3. Developmental Toxicity: One 50 mg/kg/day dosage group fetus had a domed head. No other fetus in this study was externally malformed.

C. DISCUSSION: This was a range-finding study for a developmental toxicity study in rabbits. It was adequate as conducted.

1. Maternal Toxicity: The NOEL for maternal toxicity was close to 300 mg/kg/day. The only effects observed at that dose level were a non-significant decrease in body weight gain during gestation and a significant decrease in food consumption on days 7-20 of gestation. Therefore, the NOEL is 200 mg/kg/day and the LEL is 300 mg/kg/day.

2. Developmental Toxicity: There were no observed developmental effects with this chemical at the dose levels tested. The NOEL for developmental toxicity is 300 mg/kg/day (HDT).

D. Study Deficiencies: None for a range-finding study.

E. Core Classification: Core Supplementary Data.

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DATA EVALUATION REPORT

STUDY TYPE: Teratology - Developmental Toxicity (83-3)

SPECIES: Rabbit

TOX. CHEM. NO./CASWELL NO.: 025B

ACCESSION NUMBER/MRID NO.: 412253-06

TEST MATERIAL: Pynamin Forte

SYNONYMS: D-cis/trans allethrin

STUDY NUMBER(S): KT-91-0097

REPORT NUMBER: Argus Protocol 1119-006

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, PA

TITLE OF REPORT: Teratology Study in Rabbits with Pynamin Forte

AUTHOR(S): A.M. Hoberman

REPORT ISSUED: July 17, 1989

CONCLUSION: Pynamin Forte was tested in a developmental toxicity study in rabbits. The following dose levels were used: 0, 30, 100 and 350 mg/kg/day. The NOEL for maternal toxicity is 100 mg/kg/day and the LEL is 350 mg/kg/day (death, clinical signs, decrease in body weight gain and food consumption during dosing period and gastric lesions). The NOEL for developmental toxicity is 100 mg/kg/day and the LEL is 350 mg/kg/day (increased incidences of rib/rib-vertebral malformations).

Classification: Core Guideline

Testing Guideline Satisfied: 83-3 (rabbit)

A. MATERIALS AND METHODS:

1. Test Compound(s)

Chemical Name: 36.5% allyl homolog of cinerin I and 55.5% other allethrin stereoisomers

Description: Amber colored liquid
Batch #(s), Other #(s): Lots 50310 (used through 7th day of dosing period) and 70202 (used for remainder of dosing period).
Purity: 93.4% (both)
Source: Sumitomo Chemical Company, Ltd.
Vehicle (if applicable): aqueous 0.5% (w/w) methylcellulose

2. Test Animals)

Species and Strain (sexes): Male and female New Zealand White [Hra:(NZW)SPF] rabbits
Age: 5 months at receipt.
Weight(s): 2.89 - 3.96 kg (females)
Source(s): Hazleton Research Products, Inc., Denver, PA

3. Study Design:

This study was designed to assess the developmental toxicity potential of Pynamin Forte when administered by oral intubation to rabbits on gestation days 7 through 19, inclusive.

a. Mating:

Natural or artificial insemination? artificial. Describe technique used: Each rabbit was injected with 20 USP Units/kg of Human Chorionic Gonadotropin (HCG) i.v. approximately 3 hours prior to insemination. Each rabbit was inseminated with an estimated 6.0×10^6 spermatozoa. The day artificial insemination was performed was designated as day 0 of presumed gestation. Each rabbit was artificially inseminated only once on one of four consecutive days (i.e., one fourth of the total number of rabbits assigned to each dosage group was inseminated each day).

b. Group Arrangement:

Test Group	Dosage (mg/kg/day)	Pynamin Forte Concentration (mg/ml)	Dosage Volume (ml/kg)	No. Assigned
I	0	0	10	20
II	30	3	10	20
III	100	10	10	20
IV	350	35	10	20

c. Dosing:

All doses were in a volume of 10 ml/kg of body weight/day. Dosing was based on the 7th gestation day body weight.

1) Basis For Selection of Dose Levels: Dose levels were selected on the basis of the results of the range-finding study.

2) Preparation: The appropriate amount of the test chemical was weighed out and a sufficient amount of vehicle was added to achieve a total weight of either 500 or 1000 grams. The container was capped, shaken and blended, allowed to stand to allow air bubbles to dissipate and stirred prior to dosing.

3) Frequency of Preparation: daily.

4) Storage Conditions: The test substance was kept in a cool, dry, well ventilated area and protected from heat.

5) Stability Analyses: Stability of the test substance was on file with the Sponsor and was not provided in the report.

6) Homogeneity Analyses: Conducted on the lowest and highest concentrations used in the study, ranging from 2 mg/ml to 100 mg/ml. Samples were taken from the top, middle and bottom of the sample mixture.

7) Concentration Analyses: Duplicate 10 ml samples of each prepared batch were frozen immediately after each daily preparation. One of the 2 samples taken from each concentration prepared on the first day,

tenth day, sixteenth day and the last day of dosage was sent frozen to Lancaster Laboratories, Lancaster, PA for analysis.

d. Maternal Examinations:

1) Clinical Observations and Mortality: All female rabbits were observed for appearance and general behavior daily during the prestudy period. The does were observed twice daily for viability during the acclimation, dosing and postdosing periods. Observations for clinical signs of toxicity, abortion or death were made several times each day of dosing (immediately prior to dosing, approximately 0.5 and 1 hour postdosing on days 7-19 of presumed gestation and then once daily each day of the postdosage period).

2) Body Weight Determinations: Body weights were measured weekly during acclimation, on day 0 and then daily during the dosage and postdosage periods.

3) Food Consumption: Food consumption was measured daily during throughout the study.

4) Gross Necropsy:

Animals which died or were sacrificed in moribund condition prior to end of exposure period and were subjected to complete gross pathological examinations: All does. Their uterine contents and necropsy observations were recorded. All gross lesions were preserved in formalin for possible future evaluation.

Animals sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All does. All gross lesions were preserved in formalin for possible future evaluation.

5) Uterine Examinations: The following observations were recorded:

Number of corpora lutea
Number of live fetuses
Number of dead fetuses
Early and late resorptions
Total implantations
Individual fetal weights

e. Fetal Examinations:

The fetuses were examined in the following manner: The fetuses were removed from the uterus and subsequently examined for gross external alterations. Live fetuses were sacrificed. They were all examined to identify sex and for visceral alterations; the brain was free-hand cross-sectioned (a single cut at the level of the anterior fontanelle) and examined. Abnormal fetal tissues considered appropriate for retention were preserved in neutral buffered 10% formalin. Following evisderation, the fetuses were stained with alizarin red S and evaluated for skeletal alterations. All skeletal preparations were stored in 80% glycerin with thymol crystals added to retard growth.

f. Historical Control Data:

Historical control data were provided to allow comparison with concurrent controls.

g. Statistical analysis:

The following statistical analysis methods were employed: parametric and nonparametric tests. These include Bartlett's (test for homogeneity of variance), analysis of variance (ANOVA - for homogeneous data), Dunnett's (if ANOVA significant), Kruskal-Wallis (nonparametric, not including proportion data, <= 75% ties), Dunn's test (if Kruskal-Wallis test is significant), Fisher's exact test for > 75% ties and variance test for homogeneity of the bionomial distribution (proportion data). Data obtained from nonpregnant and found dead does were excluded from statistical analyses. The litter was used as the experimental unit.

h. Compliance:

A signed Statement of Confidentiality Claim was provided (only on the basis of its falling within the scope of FIFRA). The document is considered to be confidential and trade secret information in all other countries and for all purposes other than those enunciated in FIFRA.

A signed Statement of compliance with EPA GLP's was provided.

B. RESULTS:

1. Dosage Preparation: The report stated the following: "Concentrations of dosing samples show the analytically determined concentrations for the 3 mg/ml level to range from +3.3% to -4.3% from the target concentrations; 10 mg/ml level to range from +2.0% to -2.1% and the 35 mg/ml level to range from +1.7% to -2.3% from the target concentration.

Testing of the homogeneity samples resulted in an average RSD (relative standard deviation) of 2.38% for the 2.0 mg/ml level, 5.5% for 3.0 mg/ml, 1.1% for 5.0 mg/ml, 8.56% for 60.0 mg/ml, 2.02% for 80.0 mg/ml and 1.03% for the 100 mg/ml level." The homogeneity analyses were conducted as part of another study. Analytical procedures were identical for both studies.

2. Maternal Toxicity

a. Clinical Observations and Mortality: One high dose doe died. This doe had mydriasis, tremors, clonic convulsion and lost righting reflex prior to its death on day 10 of gestation. Prior to dosing, this doe had consumed 90-156 g/day of feed and gained 0.20 kg. During the dosing period (starting on gestation day 7), this doe lost weight and exhibited decreased food consumption. This doe had 8 conceptuses that appeared to be alive and normal for their developmental ages. No other treatment-related deaths were observed. One vehicle control died from an intubation error. This doe had 9 conceptuses that appeared to be alive and normal for their developmental ages.

Other than the clinical signs observed with the doe that died, no other treatment-related clinical signs of toxicity were observed in any of the treated animals. The following is a summary of

the observed clinical signs that were not considered to be related to administration of the test substance: soft or liquid feces (1 low dose doe), red substance in cage pan (1 mid-dose dose, presumed related to early resorption of its only conceptus) and limited areas of alopecia (3, 4, 3 and 2 does in control, low dose, mid-dose and high dose groups, respectively). The NOEL for matermal mortality and clinical signs of toxicity is 100 mg/kg/day and the LEL is 350 mg/kg/day.

b. Body Weight Determinations: In the high dose group, the mean body weight gain was statistically significantly less than controls between days 7 and 10 of gestation. During the first 4 days of the post-dosage period, the mean body weight gains of both the mid- and high dose groups were statistically significantly greater than the controls. These values all appeared to be biologically significantly as well. No other treatment-related changes were observed. The NOEL for body weight gains is 100 mg/kg/day (appears to be very close) and the LEL is 350 mg/kg/day.

The investigators supplied the following data:

Table I: Body Weight Gains (Kg)[a]

Group:	Days 0-7	Days 7-10	Days 20-24	Days 24-29	Days 20-29	Days 7-20	Days 7-29	Days 0-29
Control	0.18	0.02	0.01	0.02	0.03	0.13	0.16	0.34
LDT	0.23	0.04	0.08	0.04	0.12	0.18	0.30	0.53
MDT	0.25	0.01	0.11*	0.02	0.12	0.15	0.29	0.54
HDT	0.24	-0.03*	0.11**	0.09	0.20*	0.11	0.30	0.54

* = Statistically significant $p<0.05$.
** = Statistically significant $p<0.01$.
a = Data extracted from (study KT-91-0097 or report number 1119-006 and table 5).

c. Food Consumption: The high dose group had a statistically significant decrease in food consumption relative to body weight value when compared to controls during the dosing period (days 7-17). Increases in food consumption were observed in all treated groups when compared to controls during the postdosing period. None of these increases were statistically significant, although the authors believed the increases to be biologically significant for the high dose group.

The investigators supplied the following data:

Table II: Food Consumption Data (g/kg/day)[a]

Group:	Prior to Dosing Period	Dosing Period (7-17)	Post-Dosing Period	Entire Gestation Period
Control	47.5	42.5	32.2	39.6
LDT	47.0	42.5	33.4	40.0
MDT	47.4	42.0	32.7	39.6
HDT	47.3	37.4*	37.4	39.6

[a] = Data extracted from (study KT-91-0097 or report number 1119-006 and table 7).
* = Statistically significant $p<0.05$.

d. Gross Pathology: At 350 mg/kg/day, gastric lesions (inflammation in the gastric mucosa or ulceration in the gastric pylorus) were observed in two does. The doe with the ulcerated areas had one fetus with interrelated ribs and vertebral malformations (thoracic hemivertebra, ribs that were fused and proximate at their bases and fused sternebrae). No other does showed any gross lesions related to treatment. Two other lesions were observed in treated and/or control animals. These were parovarian cysts (10, 12, 10 and 6 does in the control, low dose, mid-dose and high dose groups, respectively) and perforation of the left bronchus (control, intubation error).

e. Cesarean Section Observations: There were no treatment-related differences between the treated and control groups in the mean number of corpora lutea, implantations, resorptions and live fetuses; implantation efficiencies; percentages of live male fetuses; fetal body weights or litter sizes. One, 6, 6 and 8 pregnant does had one or more resorptions for the control, low, mid- and high dose groups, respectively. Although there appeared to be a higher rate of mean resorptions/litter in the high dose group, (0.1, 0.5, 0.4 and 1.3 resorptions/litter for controls, low, mid- and high dose groups, respectively) the authors of the report did not consider the increase to be treatment-related for the following reasons: "(1) abnormally low vehicle control group values, (2) the higher number of implantations per doe in the group given Pynamin Forte, and (3) the variation in number of pregnancies per group." It is also noted that one high dose doe had 10 resorptions in one litter

with 2 viable fetuses (12 implantation sites). This doe contributed almost half (10/21) of the total early resorptions in the high dose group. In addition, historical control data from 42 studies conducted at the test facility between 1986 and 1988 showed that the values given in this study were within the historical control range. Four hundred seventy-seven litters had an average of 0.6 resorptions/litter (range/study 0 to 1.5). One hundred seventy-eight of the 477 (37.3%) control group does had one or more resorptions (range/study = 0-10 (0-55.6%). Resorption of a single conceptus litter occurred for 9 of 477 (1.9%) does (range 0-2 (16.7%)). It appears that the increase in resorptions in the high dose group were not biologically significant. The following table summarizes the results of the study.

Table III: Cesarean Section observations[a]

	Control	LDT	MDT	HDT
Dose: (mg/kg/day)	0	30	100	350
#Animals Assigned	20	20	20	20
#Animals Mated/Inseminated	20	20	20	20
Pregnancy Rate (%)	15 (75)	19 (95)	15 (75)	18 (90)
Maternal Wastage				
#Died	1	0	0	1
#Died/pregnant	1	0	0	1
#Non pregnant	5	1	5	2
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
Corpora Lutea/Doe	9.2	11.2*	10.8*	10.4
Implantations/Doe	7.0	8.6	8.9*	7.9
Implantation Efficiency (%)[b]	78.1	75.4	83.1	77.8
Total Live Fetuses	97	153	119	113
Live Fetuses/Doe	6.9	8.0	8.5	6.6
Total Resorptions/Doe	0.1	0.5	0.4	1.3
Total Early	1	5	4	21[c]
Total Early/Doe	0.1	0.3	0.3	1.2
Total Late	0	5	2	1
Total Late/Doe	0.0	0.3	0.1	0.0
Does With Any Resorptions N(%)	1(7.1)	6(31.6)	6(42.8)	9(47.0)
Total Dead Fetuses	0	0	0	0
Mean Fetal Weight (gm/litter)	42.58	43.42	43.15	43.87
Does With Viable Fetuses	14	19	14	17
Sex Ratio (% Male)	44.0	56.6	41.4	52.8

[a] = Data extracted from (study KT-91-0097 or report number 1119-006 and tables 8 and 9).
[b] = Implantation efficiency is the number of implantation sites divided by the number of corpora lutea, multiplied by 100.
[c] = Ten of the 21 early resorptions were from one litter.
* = Significantly different from control ($p<=0.05$).

3. Developmental Toxicity: In the high dose group, an increase in the incidences of rib/rib-vertebral malformations was observed when compared to the control group. These increases were not statistically significant when the analyses were based only on live day-29 Caesarean-delivered fetuses (P>0.05). However, inclusion of one high dose group late resorption that also had this malformation resulted in statistical significance (p<=0.01) for the high dose group litter and fetal incidences. The incidence also exceeded the historical control range. There were no other observed compound-related alterations in either the external, soft tissue or skeletal examinations. The following tables summarize the results.

Table IV: External Examinations

Observations[+]	Control	Low Dose	Mid Dose	High Dose
#pups(litters) examined	97(14)	153(19)	119(14)	113(17)
#pups(litters) affected	0(0)	0(0)	0(0)	0(0)

Table V: Visceral Examinations

Observations[+]	Control	Low Dose	Mid Dose	High Dose
#pups(litters) examined	97(14)	153(19)	119(14)	113(17)
Eye				
Right, circumcorneal hemorrhage	0(0)[a]	1(1)	0(0)	0(0)
Lungs				
Intermediate lobe, agenesis	2(1)	0(0)	0(0)	1(1)

([+]) some observations may be grouped together
([a]) fetal [litter] incidence

Table VI: Skeletal Examinations

Skeletal examination revealed rib-vertebral malformations in 1 control fetus, 1 low-dose fetus and in 6 high dose group specimens from 6 different litters (5 were live fetuses and 1 was a late resorption) (see the fourth page of the table). As stated before, the incidences in the high dose group were statistically significant if the resorption is included. The following tables are taken directly from the report.

TABLE 13 (PAGE 1): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
SKULL - IRREGULAR OSSIFICATION[b] (V)					
(SUMMARIZATION OF ALL IRREGULAR OSSIFICATION OF SKULL[c]; SUMMARIZED AND INDIVIDUAL SUBCATEGORIES CITED BELOW)					
Litter Incidence	N(%)	10(71.4)	16(84.2)	12(85.7)	12(70.6)
Fetal Incidence	N(%)	22(22.7)	42(27.4)	29(24.4)	33(29.2)
NASAL(S), IRREGULAR OSSIFICATION (V) (SUMMARIZATION OF INTERNASAL, INTRANASAL, IRREGULAR SUTURE, MIDLINE SUTURE DISPLACED, FUSED, NASAL-FRONTAL, SUTURE(S) IRREGULAR)					
Litter Incidence	N(%)	7(50.0)	13(68.4)	10(71.4)	8(47.0)
Fetal Incidence	N(%)	16(16.5)	23(15.0)	17(14.3)	18(15.9)
Nasals, Internasal (V)					
Litter Incidence	N(%)	1(7.1)	0	0	1(5.9)
Fetal Incidence	N(%)	2(2.1)	0	0	1(0.9)
Nasal(s), Intranasal(s) (V)					
Litter Incidence	N(%)	1(7.1)	1(5.3)	1(7.1)	0
Fetal Incidence	N(%)	1(1.0)	1(0.6)	1(0.8)	0
Nasals, Irregular Suture (V)					
Litter Incidence	N(%)	0	1(5.3)	1(7.1)	2(11.8)
Fetal Incidence	N(%)	0	1(0.6)	1(0.8)	2(1.8)
Nasals, Midline Suture, Displaced (V)					
Litter Incidence	N(%)	5(35.7)	8(42.1)	4(28.6)	6(35.3)
Fetal Incidence	N(%)	7(7.2)	11(7.2)	7(5.9)	10(8.8)[a]

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TABLE 13 (PAGE 2): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
SKULL - IRREGULAR OSSIFICATION (CONTINUED)[b]					
Nasals, Fused (V)					
Litter Incidence	N(%)	0	1(5.3)	0	0
Fetal Incidence	N(%)	0	1(0.6)	0	0
Nasal-Frontal, Suture(s) Irregular (V)					
Litter Incidence	N(%)	4(28.6)	8(42.1)	5(35.7)	5(29.4)
Fetal Incidence	N(%)	7(7.2)[e]	9(5.9)	9(7.6)[h,j,k]	7(6.2)[m]
FRONTAL(S), IRREGULAR OSSIFICATION (V) (SUMMARIZATION OF INTERFRONTAL, INTRAFRONTAL, IRREGULAR SUTURE, ENLARGED)					
Litter Incidence	N(%)	8(57.1)	11(57.9)	7(50.0)	10(58.8)
Fetal Incidence	N(%)	14(14.4)	19(12.4)	15(12.6)	22(19.5)
Frontals, Interfrontal (V)					
Litter Incidence	N(%)	2(14.3)	7(36.8)	4(28.6)	6(35.3)
Fetal Incidence	N(%)	2(2.1)	8(5.2)	4(3.4)	8(7.1)[m,n]
Frontal(s), Intrafrontal(s) (V)					
Litter Incidence	N(%)	1(7.1)	1(5.3)	1(7.1)	1(5.9)
Fetal Incidence	N(%)	3(3.1)	1(0.6)	1(0.8)	2(1.3)
Frontals, Irregular Suture (V)					
Litter Incidence	N(%)	8(57.1)	9(47.4)	6(42.8)	7(41.2)
Fetal Incidence	N(%)	8(8.2)	11(7.2)[i]	11(9.2)[j]	13(11.5)[l,q]

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TABLE 13 (PAGE 3): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
SKULL - IRREGULAR OSSIFICATION (CONTINUED)[b]					
Frontal, Suture, Enlarged (V)					
Litter Incidence	N(%)	1(7.1)	0	0	0
Fetal Incidence	N(%)	1(1.0)[e]	0	0	0
PARIETAL(S), IRREGULAR OSSIFICATION (V) (SUMMARIZATION OF INTRAPARIETAL, IRREGULAR SUTURE)					
Litter Incidence	N(%)	2(14.3)	5(26.3)	3(21.4)	2(11.8)
Fetal Incidence	N(%)	3(3.1)	7(4.6)	4(3.4)	2(1.8)
Parietals, Interparietal (V)					
Litter Incidence	N(%)	2(14.3)	5(26.3)	2(14.3)	1(5.9)
Fetal Incidence	N(%)	3(3.1)	7(4.6)	3(2.5)[f]	1(0.9)
Parietals, Irregular Suture (V)					
Litter Incidence	N(%)	0	0	1(7.1)	1(5.9)
Fetal Incidence	N(%)	0	0	1(0.8)	1(0.9)
SKULL - OTHER ALTERATIONS					
Premaxillae, Incompletely Ossified (V)					
Litter Incidence	N(%)	1(7.1)	0	0	0
Fetal Incidence	N(%)	1(1.0)[e]	0	0	0
Frontal(s), Contain Holes (V)					
Litter Incidence	N(%)	1(7.1)	0	1(7.1)	0
Fetal Incidence	N(%)	1(1.0)	0	1(0.8)	0

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TABLE 13 (PAGE 4): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
MYOID[b]:					
Ala(e), Angulated (V)					
Litter Incidence	N(%)	3(21.4)	6(31.6)	2(14.3)	3(17.6)
Fetal Incidence	N(%)	3(3.1)	9(5.9)g	7(5.9)j,k	3(2.6)o
Body, Not Ossified (V)					
Litter Incidence	N(%)	0	1(5.3)	0	0
Fetal Incidence	N(%)	0	1(0.6)	0	0
RIB/RIB-VERTEBRAL MALFORMATIONS:					
Includes: Vertebrae - Thoracic, hemivertebra; Thoracic, centra/arches, fused; Thoracic, centra, unilateral ossification; Thoracic, centrum, bifid; Thoracic, centrum, asymmetric; Ribs - fused or split					
Litter Incidence	N(%)	1(7.1)	1(5.3)	1(7.1)	5(29.4)
Fetal Incidence	N(%)	1(1.0)d	1(0.5)f	1(0.8)	5(4.4)n,o,p,q,r
Vertebrae:					
Thoracic, Hemivertebra (Arch and/or Centrum with Attached Rib) (M)					
Litter Incidence	N(%)	0	0	0	3(17.6)
Fetal Incidence	N(%)	0	0	0	3(2.6)n,q,r
Thoracic, Centra/Arches, Fused (M)					
Litter Incidence	N(%)	1(7.1)	0	0	1(5.9)
Fetal Incidence	N(%)	1(1.0)d	0	0	1(0.9)r

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TABLE 13 (PAGE 5): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
Vertebrae (Continued):					
Thoracic, Centrum, Unilateral Ossification (M)					
Litter Incidence	N(%)	1(7.1)	1(5.3)	0	1(5.9)
Fetal Incidence	N(%)	1(1.0)[d]	1(0.6)[f]	0	1(0.9)[p]
Thoracic, Centrum, Bifid (M)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)[p]
Thoracic, Centrum, Asymmetric (M)					
Litter Incidence	N(%)	0	1(5.3)	0	2(11.8)
Fetal Incidence	N(%)	0	1(0.6)[f]	0	2(1.8)[p,r]
Rib(s):					
Two or More, Fused (M)					
Litter Incidence	N(%)	1(7.1)	1(5.3)	0	3(17.6)
Fetal Incidence	N(%)	1(1.0)[d]	1(0.6)[f]	0	3(2.6)[p,q,r]
Split (M)					
Litter Incidence	N(%)	0	0	0	2(11.8)
Fetal Incidence	N(%)	0	0	0	2(1.8)[n,o]
Extra Rib Present (M)					
Litter Incidence	N(%)	0	1(5.3)	0	0
Fetal Incidence	N(%)	0	1(0.6)	0	0

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TABLE 13 (PAGE 6): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
Rib(s) (Continued):					
Short (M)					
Litter Incidence	N(%)	0	0	1(7.1)	0
Fetal Incidence	N(%)	0	0	1(0.8)	0
Proximate at Bases (M)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)q
VERTEBRAE:					
Caudal, Fused (M)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)p
Caudal, Misaligned (V)					
Litter Incidence	N(%)	0	0	2(14.3)	0
Fetal Incidence	N(%)	0	0	2(1.7)k	0
RIB(S):					
Thickened Areas (V)					
Litter Incidence	N(%)	0	1(5.3)	2(14.3)	0
Fetal Incidence	N(%)	0	1(0.6)g	2(1.7)j	0

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TABLE 13 (PAGE 7): FETAL SKELETAL ALTERATIONS - SUMMARY
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Evaluated	N	14	19	14	17
Specimens Evaluated[a]	N	97	153	119	114
Fetuses	N	97	153	119	113
Live	N	97	153	119	113
Dead	N	0	0	0	0
Late Resorptions[a]	N	0	0	0	1
MANUBRIUM:					
Incompletely Ossified (V)					
Litter Incidence	N(%)	0	1(5.3)	0	0
Fetal Incidence	N(%)	0	1(0.6)[f]	0	0
STERNEBRAE:					
Two or More, Fused (V)					
Litter Incidence	N(%)	1(7.1)	2(10.5)	3(21.4)	4(23.5)
Fetal Incidence	N(%)	1(1.0)[e]	2(1.3)	4(3.4)[h,i]	5(4.4)[l,m,r]
Asymmetric (V)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)[r]
Incompletely Ossified (V)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)[r]
SCAPULAE:					
Alae, Irregularly Shaped (V)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)
REAR LIMB:					
Right, Tibia, Thin, Fibula, Not Ossified (M)					
Litter Incidence	N(%)	0	0	0	1(5.9)
Fetal Incidence	N(%)	0	0	0	1(0.9)P

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TABLE 13 (PAGE 8): FETAL SKELETAL ALTERATIONS - SUMMARY

FOOTNOTES

a. Observations for the late resorption were excluded from statistical analyses. The observations are cited on Table 22.

b. Fetuses with alterations in ossification of the skull and/or hyoid are not separately identified in this summary table, except when alterations in other ossification sites were also present.

c. Includes all findings noted for the skull except frontals, contain holes and hyoid, ala(e), angulated. These categories are excluded because each is not considered irregular ossification of the skull.

d. Fetus 13133-11 also had other skeletal alterations.

e. Fetus 13143-1 also had other skeletal alterations.

f. Fetus 13158-6 also had other skeletal alterations.

g. Fetus 13158-7 also had other skeletal alterations.

h. Fetus 13177-8 also had other skeletal alterations.

i. Fetus 13179-7 also had other skeletal alterations.

j. Fetus 13187-5 also had other skeletal alterations.

k. Fetus 13187-6 also had other skeletal alterations.

l. Fetus 13195-4 also had other skeletal alterations.

m. Fetus 13195-6 also had other skeletal alterations.

n. Fetus 13201-5 also had other skeletal alterations.

o. Fetus 13205-6 also had other skeletal alterations.

p. Fetus 13206-6 also had other skeletal alterations.

q. Fetus 13208-2 also had other skeletal alterations.

r. Fetus 13209-1 also had other skeletal alterations.

** Significantly different from the vehicle control group value ($P \leq 0.01$).

(M) = Malformation

(V) = Variation

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TABLE 14 (PAGE 1): FETAL OSSIFICATION SITES (LIVEBORN FETUSES - DAY 29)

		Dosage Group (mg/kg/days 7-19 of Gestation)			
		0(Vehicle)	30	100	350
Litters Examined	N	14	19	14	17
Fetuses Examined	N	97	153	119	112
Ossification Sites/Litter					
Hyoid	$\bar{X}$±S.D.	0.98 ± 0.05	0.98 ± 0.05	0.99 ± 0.03	0.99 ± 0.05
Cervical (VERTEBRAE)	$\bar{X}$±S.D.	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00
Thoracic (VERTEBRAE)	$\bar{X}$±S.D.	12.56 ± 0.32	12.54 ± 0.32	12.55 ± 0.28	12.69 ± 0.22
Lumbar (VERTEBRAE)	$\bar{X}$±S.D.	6.41 ± 0.32	6.44 ± 0.32	6.45 ± 0.26	6.29 ± 0.22
Sacral (VERTEBRAE)	$\bar{X}$±S.D.	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00
Caudal (VERTEBRAE)	$\bar{X}$±S.D.	17.03 ± 0.45	16.94 ± 0.51	16.82 ± 0.38	17.22 ± 0.39
Ribs	$\bar{X}$±S.D.	12.48 ± 0.33	12.45 ± 0.34	12.47 ± 0.27	12.62 ± 0.23
Manubrium (STERNUM)	$\bar{X}$±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00
Sternal (STERNUM)	$\bar{X}$±S.D.	3.96 ± 0.09	3.93 ± 0.15	3.91 ± 0.17	3.96 ± 0.08
Xiphoid (STERNUM)	$\bar{X}$±S.D.	0.96 ± 0.07	0.95 ± 0.11	0.95 ± 0.12	0.95 ± 0.10
Forepaws					
Carpals	$\bar{X}$±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Metacarpals	$\bar{X}$±S.D.	4.96 ± 0.11	4.98 ± 0.05	4.96 ± 0.07	5.00 ± 0.00
Digits	$\bar{X}$±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
Phalanges	$\bar{X}$±S.D.	13.97 ± 0.11	13.85 ± 0.25	13.98 ± 0.06	13.92 ± 0.14
Hindpaws					
Tarsals	$\bar{X}$±S.D.	2.00 ± 0.00	1.98 ± 0.07	2.00 ± 0.00	1.98 ± 0.05
Metatarsals	$\bar{X}$±S.D.	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
Digits	$\bar{X}$±S.D.	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00	4.00 ± 0.00
Phalanges	$\bar{X}$±S.D.	11.98 ± 0.05	12.00 ± 0.00	12.00 ± 0.00	12.00 ± 0.00

Historical Control Data for Rib-Vertebral Malformations: In 27 studies conducted at the Test Facility between 1986 and 1988, rib/vertebral malformations occurred in 26 of 3039 fetuses [0.8%; range = 0 to 3 (2.52%) per study] and in 24 of 425 litters [5.6%; range = 0 to 3 (18.3%) per study].

C. DISCUSSION:

1. Maternal Toxicity: In the high dose group there was one death. This doe exhibited mydriasis, tremors, clonic convulsions and lost righting reflex prior to death. There was a decrease in body weight gain and food consumption during the dosing period and 2 does in this dose group had gastric lesions.

2. Developmental Toxicity:

   a. Deaths/Resorptions: No treatment-related differences between treated and control fetuses.

   b. Altered Growth: No treatment-related differences between treated and control fetuses.

   c. Developmental Anomalies: No treatment-related differences between treated and control fetuses.

   d. Malformations: At the highest dose level, there was an increase in the incidences of rib/rib-vertebral malformations.

D. Study Deficiencies: None.

E. Core Classification: Core Guideline Data.

Maternal NOEL = 100 mg/kg/day
Maternal LOEL = 350 mg/kg/day
Developmental Toxicity NOEL = 100 mg/kg/day
Developmental Toxicity LOEL = 350 mg/kg/day

END